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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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NGUYEN, Q	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/151,612	Applicant(s) KOHN ET AL.	
	Examiner Quang Nguyen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18,21-26,29-60,62,67-78 and 80-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-18,21-26,29-60,62,67-78 and 80-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed July 23, 2001 in Paper No. 14 has been entered.

Claims 1-2, 4-18, 21-26, 29-60, 62, 67-78 and 80-83 are pending in the present application. However, claims 1-2, 4-18, 21-26, 29-35, 42-46, 60, 62, 74-78 and 80-83, drawn to the elected invention, are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Most of the references cited in the IDS filed on 3/19/1999 in Paper No. 5 have not been considered because they were unavailable with the application.

Upon further reconsideration of the application, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 1-2, 4-18, 21-26, 29-35, 42-46, 60, 62, 74-78 and 80-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) An *in vitro* method of increasing immune recognition of a mammalian cell by introducing a sequence non-specific double-stranded polynucleotide greater than 25 nucleotides in length into the cell and thereby activating expression of a gene or gene product comprising MHC class I, MHC class II, TAP-1, TAP-2, a proteasome subunit, HLA-DM, invariant chain, a B7 co-stimulatory molecule, PKR, IFN-β, MAP kinase, NF-κ,

JAK, STATS, wherein said activation increases the ability of said cell to present antigen to an immune cell;

(b) A method for inducing an autoimmune disease mimicking the human Graves' disease in a mouse, said method comprises introducing a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into a syngeneic murine cell expressing a functional full-length human thyrotropin receptor (TSHR) *in vitro*, and introducing said murine cell into said mouse;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1, 2, 4-18, 23-25 and 43-44 are directed to a method of increasing immune recognition of a mammalian cell by artificially introducing a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into the cell and thereby activating expression of a group of gene or gene product as recited in the claims, wherein said activation increases the ability of said cell to present antigen to

an immune cell. Claims 21, 22, 26, 42 and 45 are drawn to the same method further comprising introducing said cell into a host organism.

Claims 74, 75, 29-35 and 46 are drawn to a method for increasing presentation of an antigen by a mammalian cell comprising: (a) introducing a sequence non-specific double-stranded polynucleotide greater than 25 nucleotides in length into the mammalian cell *ex vivo*, which causes the cell to have an increased ability to present antigen, (b) increasing the mammalian cell's ability to present antigen and forming an activated antigen presenting cell (APC), and (c) measuring an increase in expression of an MHC molecules or a co-stimulatory molecule; the same method further comprising introducing the activated APC into a host animal.

Claims 60 and 62 are drawn to a method for treating a mammalian disease which is sensitive to immunotherapy which comprises: (a) removing diseased cells from a mammal; (b) introducing a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into the cells; (c) treating the cells to prevent division permitting other metabolic activity; and (d) immunizing the mammal with an effective amount of the cells to prevent or alleviate the symptoms of the disease; the same method used to enhance another treatment method that enhances an immune response or an antigen presentation.

Claims 76 and 80-82 are directed to a method for treating cancer or a mammalian infectious disease which is associated with immunodeficiency (AIDS as a preferred embodiment) with a vaccine comprising a somatic mammalian cell with the enhanced ability to present antigen to the immune system, comprising: (a) introducing

a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into the somatic mammalian cell *ex vivo*, which causes the cell to have an increased ability to present antigen; (b) measuring an increase in expression of a MHC molecule or a co-stimulatory molecule involved in antigen presentation selected from the group consisting of TAP-1, TAP-2, a proteosome subunit, HLA-DM, invariant chain, CIITA, RFX5, B7 co-stimulatory molecule, PKR, IFN-beta, MAP kinase, NFκB, JAK and a STAT; and (c) preparing the mammalian cell for immunization; the same method that is co-ordinated with a treatment with CpG residues used to enhance immune cell responsiveness.

Claims 77, 78 and 80 are directed to a method for treating cancer which is sensitive to immunotherapy which comprises: (a) removing a diseased cells from a mammal; (b) increasing or decreasing the expression of antigen by the cell; and (c) immunizing the mammal with an effective amount of the cell to prevent or alleviate the symptoms of the disease; the same method is used to enhance another treatment method that enhance an immune response or an antigen presentation.

The specification teaches that any double stranded (ds) nucleic acid fragment introduced *in vitro* into the cytoplasm of non-immune cells or leakage of self DNA caused by environmentally induced damage can induce MHC gene expression directly and the expression of other essential genes and gene products important for antigen processing and antigen presentation. The effect is sequence-independent, is not duplicated by single stranded nucleic acids, and it is different and additive to that of γIFN. The specification further discloses that ds-polynucleotides can induce the

expression of the 90K tumor-associated immunostimulator implicated in host mechanisms to defend against tumors and AIDS, and that ds-polynucleotides regulate cell cycle progression and growth, and their regulation mechanism is different from that of γIFN. Additionally, the specification teaches that mice immunizing with syngeneic fibroblasts transfected *in vitro* with ds-polynucleotides and a functional thyrotropin receptor (TSHR), were induced to develop an autoimmune disease with features mimicking the human Grave's disease.

The above evidence has been noted and considered. However, the evidence can not be reasonably extrapolated to the instant broadly claimed invention which when read in light of the specification encompass an *in vivo* method of increasing immune recognition of a mammalian cell by introducing a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into a cell and an *ex vivo* method of increasing presentation of antigen by a cell for immunization purpose to treat or prevent various autoimmune conditions and diseases, among which are cancer and AIDS (See specification, page bottom paragraph of page 44 to the top paragraph of page 45, and see the claims). This is because the mere upregulation of MHC, genes and gene products involved in antigen processing and antigen presentation, and 90K tumor-associated immunostimulator by ds-polynucleotides in cells *in vitro* and the generation of mice having an autoimmune disease with features mimicking the human Grave's disease are not deemed to correlate with any protective or therapeutic immune responses contemplated by Applicants. There is no evidence of record indicating that cells transfected *in vitro* with a sequence non-specific double-stranded polynucleotide

greater than 25 nucleotides in length would be able to present a suitable antigen having antigenic epitopes *in vivo* to B and/or T cells that would recognize and kill tumor cells or infectious viruses such as HIV having the same antigenic epitopes to yield the therapeutic effects contemplated by Applicants. More recently, it has been observed that activated and mature dendritic cells or APCs can not even processed certain antigenic peptides or epitopes mainly of self origin including tumor epitopes to activate the effector cytotoxic T lymphocytes *in vivo* (van den Eynde et al., Curr. Opin. Immunol. 13:147-153, 2001).

The specification is not enabled for the instant broadly claimed invention because the specification fails to provide guidance for a skilled artisan on how to deliver *in vivo* a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into a cell in a host to induce an effective immune response for immunization purposes or for producing any and all autoimmune reactions that have beneficial uses. Nor does the specification provide sufficient guidance for an *ex vivo* method to induce an effective immune response in a host for recognizing and killing tumor cells or infectious agents such as HIV. The specification does not teach the dosage amounts, frequency, or routes of administering ds-polynucleotides or cells transfected with ds-polynucleotides into a host to generate desired therapeutic results for any specific autoimmune conditions or diseases. The mere upregulation of MHC, genes and gene products involved in antigen processing and antigen presentation, and 90K tumor-associated immunostimulator by ds-polynucleotides in cells *in vitro* and the generation of mice having an autoimmune disease with features mimicking the human Grave's

disease are not deemed to correlate with any protective or therapeutic immune responses contemplated by Applicants. Since the prior art does not teach such a correlation, it is incumbent upon the instant application to do so. In the absence of such guidance, it would have required undue experimentation without an expectation of success for one skilled in the art to make and use the claimed invention.

With respect to claims encompassing an *in vivo* method, the nature of the claims would fall within the realm of genetic immunization which at the effective filing date of the present application was still immature and highly unpredictable. Regarding to the state of the art of genetic vaccines, Chattergoon et al. (FASEB J. 11:753-763, 1997) noted that although DNA vaccines have shown promises in animal models and have raised hopes, the technology is still considered to be an "emerging" technology (column 1, paragraphs 2 & 3, page 762). More recently, Leitner et al. (Vaccine 18:765-777, 2000) stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). It is well recognized that the animal model should correlate to the disease condition studied, and the route of administration as being a critical parameter determining whether protective immunity is elicited. One of skilled in the art would have also have recognized that results observed in animal model systems are not predictive of outcome or efficacy in applications in other species of animal or in humans, due to differences in anatomy, cell biology, genetics and immunology between different types of animals, and between the animal models and humans (See page 79 in Ledley F.D., Hum. Gen. Ther. 2:77-83, 1991).

This is further supported by the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (col. 2, last paragraph, page 296). It is noted that the sequence non-specific double-stranded polynucleotides greater than 25 nucleotides in length recited in the instant claims would encompass any and all vectors used in the prior arts. Moreover, the instant disclosure has not provided any evidence that reasonably correlate to the effective protective immune responses and/or the desired therapeutic results contemplated by Applicants have been attained, not even in any relevant animal model. In the absence of such teachings provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

An embodiment of the claims encompassing an *in vivo* method requires the introduction of a ds-polynucleotide into a particular cell (cell expressing an autoantigen, see claim 12) or specific cell types (non-immune cell, immune cell, antigen presenting cell, thyroid cell or tumor cell, see claims 13 and 75). As written, the claims encompass any and all routes of delivery a sequence non-specific ds-polynucleotide greater than 25 nucleotides in length into the desired cells in a host. Vector targeting *in vivo* to desired cells or tissues or organs continues to be unpredictable and inefficient. This is supported by numerous teachings in the art, particularly in the art of gene therapy.

Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the main obstacles hampering a successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time." (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promises. One of which is the ligand-targeted receptor-mediated vector approach with a relatively higher level of tissue specificity than viruses can offer. However, this approach to gene therapy is much less efficient than viral gene delivery (col. 1, last paragraph, page 65). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They also indicated clearly that resolution to vector targeting *in vivo* had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting an efficient targeting of viral vectors such that an efficient delivery of a transgene, for this instance a ds-polynucleotide, has not been achieved (see page 239, and second and third columns of page 242). The instant specification fails to teach one of skill in the art how to overcome the unpredictability of vector targeting *in vivo* or more specifically an effective delivery of a sequence non-specific ds-polynucleotide to targeted cells could be achieved by any and all modes of delivery to yield the desired immune responses contemplated by Applicants. As an example, could an intravenous delivery of an effective amount of a sequence non-specific ds-polynucleotide to a solid tumor cell be achieved in the presence of DNAases in the blood? Would any and all sequence non-specific ds-polynucleotides be stable in the blood long enough without being degraded

prior to be taken up by desired targeted cells? Given the lack of sufficient guidance provided by the instant disclosure, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

With regard to claims drawn to an *ex vivo* method, there are several questions that need to be addressed, such as, "What is the minimum proportion of cells or tumor cells transfected with a sequence non-specific ds-polynucleotide required to induce an effective protective or therapeutic immune response, or a desired autoimmune response in a host to generate various relevant models of specific and autoimmune conditions or diseases?", "To which host tissues do the transfected cells home in and how long do they need to stay in the system of the host to induce desired immune responses contemplated by Applicants?", "Which route of delivery of these transfected cells is effective to obtain the desired immune responses?", "How stable is the state of activated antigen presenting for cells transfected with a sequence non-specific ds-polynucleotide such that the appropriate and specific B and T cells can be activated to yield the desired immune responses contemplated by Applicants?". It is further noted for certain claims (for examples, claims 21, 22, 26, 42, 45 46, 76, 80-82), their scope encompasses the use of xenogeneic as well as allogeneic cells transfected with a sequence non-specific ds-polynucleotide. However, it is well known in the art of transplantation that the administration of such xenogeneic and allogeneic cells into a host would result in vigorous and deleterious immune rejection reactions. As such, it is unclear whether the administered transfected cells would last long enough to mediate an effective activation of B and T cells specific for the desired antigen (tumor or HIV)

that results in therapeutic immune responses contemplated by Applicants. With the lack of sufficient guidance provided by the specification regarding to the aforementioned issues, particularly there is no evidence of record showing any therapeutic or protective immune response has been attained, it would therefore require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Apart from the teachings provided by the instant disclosure regarding to the generation of a mouse model having features mimicking the human autoimmune Graves' disease, the specification fails to provide sufficient guidance or direction for the generation of any and all other relevant autoimmune disease models. Relevant information such as the specific co-transfected gene encoding for an antigen (thyrotropin receptor for the disclosed mouse model), the promoter, the vector construct used to express said antigen, the cell dosage used, the frequency and route of administering utilized to generate other specific autoimmune disease models are absent. It should be noted that guidance for overcoming known differences in anatomy, cell biology, genetics and immunology between different types of animals has not been provided by the instant specification for making any and all animal models with desired autoimmune diseases. Moreover, it should be noted that the development of an autoimmune disease involves a complex interaction between predisposing genes and environmental triggers as evidenced by the teachings of Tomer et al. with regard to autoimmune thyroid diseases in a post-filing art (J. Clin. Endocrinol. Metab. 84: 4656-4664, 1999). Additionally, the CAFC has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or

may be workable". The Appeal court continues to state that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech, Inc. v. Novo Nordisk A/S*, 42 USPQ 2d 1001, at 1005). With the lack of guidance provided by the instant disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

With respect to claim 46, as written the instant specification is not enabled for the method as claimed. This is because the specification fails to provide any guidance for a skilled artisan on how to measure an increase in expression of a MHC molecule or a co-stimulatory molecule in the transfected somatic mammalian cell in the immune system of a mammal. Applicants are invited to point out specifically in the present specification where such teachings are provided. With the lack of guidance provided by the instant disclosure in this regard, it would certainly required undue experimentation for one skilled in the art to make and use the method as claimed.

With regard to claims 77, 78 and 83, the specification fails to teach specifically the parameters involved in the increasing or decreasing expression of an antigen in a cell, a particular antigen for treating any and all cancers in the methods as claimed. Furthermore, it is totally unclear how decreasing the expression of an antigen in a diseased cell in the claimed methods would result in the prevention and alleviation the symptoms of cancer. Additionally, because of the complex nature of the cytokine network and its interaction between various immune cells which play an integral part of

augmenting the effector function to yield therapeutic effects in an immunotherapy are not readily predictable, with the lack of guidance provided by the instant specification it would have required undue experimentation for one skilled in the art to make and use the methods as claimed, let alone these methods have any additional or synergistic therapeutic effects in conjunction with other available treatment methods. Moreover, the physiological art has been recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With respect to claims encompassing *in vivo* and *ex vivo* scopes, it is further noted that there is no evidence of record indicating that cells transfected with a sequence non-specific double-stranded polynucleotide greater than 25 nucleotides in length would present a suitable antigen having antigenic epitopes to B and/or T cells that would recognize and kill tumor cells or infectious viruses such as HIV having the same antigenic epitopes to yield the therapeutic effects contemplated by Applicants. Recently, it has been observed that activated and mature dendritic cells or APCs can not processed certain antigenic peptides or epitopes mainly of self origin including tumor epitopes to activate the effector cytotoxic T lymphocytes (van den Eynde et al., Curr. Opin. Immunol. 13:147-153, 2001). As such, with the lack of guidance provided by the instant disclosure, it would have required undue experimentation for a skilled

artisan to make and use the instant broadly claimed invention. Lastly, it is noted that in a normal host, there is a regular turnover of cells including cells having leakage of DNA from the cell's nucleus or mitochondria and yet the host is not immunized from viral infections or cancer. Furthermore, there is also a high turnover of tumor cells in a tumor as well as elevated levels of 90K immunostimulator in serum of patients suffering from various types of cancer and AIDS (Brakebusch et al., J. Biol. Chem. 272:3674-3682, 1997; PTO-1449, # 15) and yet the mere presence of the 90K immunostimulator or the presence of a sequence non-specific ds-polynucleotide in a tumor cell due to leakage from the cell's nucleus or mitochondria are not sufficient to give the patients any therapeutic effects.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the genetic immunization art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on July 23, 2001 in Paper No. 14 (pages 6-21) have been fully considered.

Applicants mainly argued that the procedure used to create the Graves mouse model can be adapted to develop protective immune responses in other animal models including human, and that autoimmunity is a protective response. Applicants further argued that the instantly claimed invention produces a protective response in tumors,

specifically the thyroid tumor model, by referring to the attached reference of Iishi and co-workers (page 7, first full paragraph). Applicants also stated that "Applicants have practiced the instantly claimed invention and used the identical procedure to express tumor autoantigens that prevent a thyroid tumor from developing and growing as well as a standard injection procedure to develop an antibody response that exceeds a known adjuvant protocol. This research is disclosed in the references attached hereto" (page 8, first paragraph). Examiner respectfully finds Applicant's arguments to be unpersuasive because none of the cited references related to the autoimmune thyroid diseases indicates or suggests the immune responses induced as a result of an artificially introduction of a sequence non-specific double-stranded polynucleotide greater than 25 nucleotides in length into a mammalian cell would be effective to prevent or to treat cancer or viral diseases associated with immunodeficiency such as AIDS as contemplated by Applicants. The reference of Iishi and co-workers (which journal?) and references (which journals?) that Applicants asserted to use the same procedure of the instant invention to express tumor autoantigens to prevent a thyroid tumor from developing and growing are not provided. Therefore, Examiner can not evaluate whether the therapeutic results contemplated by Applicants have been attained by the methods of the instant invention, nor can Examiner evaluate Applicants' comments on the cited reference of Chattergoon et al.

With respect to the cited reference of Ledley, Applicants argued that the quote from Ledley is taken out of context. Applicants argued that "Ledley discloses virus targeting and suggests that animal experiments are not predictive because animals do

not have the viral attachement site. In no way does Ledley otherwise negate the importance of animal models. Thus, animal experiments if positive are often predictive of success in human." (page 14, last paragraph continues to page 15). Examiner respectfully finds Applicants' arguments to be unpersuasive because it is Applicants' assertion that animal experiments if positive are often predictive of success in human without any factual evidence indicating or suggesting that the therapeutic results contemplated by Applicants could be attained in any suitable animal model that commensurates with the scope of the instant claimed invention. Furthermore, please also note the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (col. 2, last paragraph, page 296).

Applicants further argued that Examiner has placed an unreasonable burden on Applicants that they must prove that the invention is applicable in any and all subjects (page 15, first full paragraph). This is not found to be persuasive because there is no evidence of record indicating that any therapeutic end results contemplated by Applicants could be reasonably attained in any suitable animal model that commensurates with the scope of the present claimed invention.

With respect to the issues of routes of delivery or targeted cells, Applicants' arguments on page 16 of the Amendment C are not relevant to claims encompassing an *in vivo* method such as claims 1-2, 4-18, 26, for examples.

With regard to the issues related to claims directed to an *ex vivo* method, Applicants mainly refer to the teachings found in the Shimojo model on the induction of Graves-like disease in mice. However, Examiner respectfully does not find a nexus or a reasonable correlation between an immune response responsible for Graves-like disease with an effective immune response required for the protection and treatment of tumor and/or viral infectious diseases such as AIDS as contemplated by Applicants. Although Applicants asserted that effective therapeutic or protective immune response has also been demonstrated in a tumor model, the relevant article has not been provided to Examiner for consideration.

With respect to the issue of other autoimmune disease models apart from the Shimojo mouse model of human autoimmune Graves' disease, Applicants argued that the Shimojo model has been adapted to produce autoimmune thyroiditis using TPO as an autoantigen as evidenced by the teachings of Jaume et al. (J. Clin. Endocrinol. Metabol. 84:1651-1657, 1999). Therefore, Applicants argued that the Shimojo model is applicable for other autoimmune responses, and not only to Graves' disease. Examiner respectfully finds Applicants' arguments to be unpersuasive. Firstly, the instant specification has no support for the use of TPO as an autoantigen in the generation of the autoimmune thyroiditis in the post-filing art of Jaume et al. Secondly, there is no evidence of record indicating that other autoimmune disease models (e.g., diabetes,

arthritis and others) could be generated on the basis of the instant disclosure. It is further noted that the development of an autoimmune disease involves a complex interaction between predisposing genes and environmental triggers as evidenced by the teachings of Tomer et al. with regard to autoimmune thyroid diseases in a post-filing art (J. Clin. Endocrinol. Metab. 84: 4656-4664, 1999). With the lack of sufficient guidance provided by the present specification, it would therefore have required undue experimentation for a skilled artisan to make and use the full scope of the instant claimed invention.

With respect to claim 77 regarding to the issue that the specification fails to teach specifically the parameters involved in the increasing or decreasing expression of an antigen in a cell, Applicants argued that the specification teaches the parameters and show that tumor antigen does not need to be defined. Additionally, Applicants referred to Fig. 5 of the specification and the Molteni reference. Examiner respectfully finds Applicants' arguments to be unpersuasive because they are not directed to how an antigen expression is increased or decreased as recited in the claim, such that therapeutic effects contemplated by Applicants could be obtained. Particularly, it is totally unclear how decreasing the expression of an antigen in a diseased cell in the claimed methods would result in the prevention and alleviation the symptoms of cancer.

Accordingly, claims 1-2, 4-18, 21-26, 29-35, 42-46, 60, 62, 74-78 and 80-83 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-18, 21-26, 29-35, 42-46, 74-78 and 80-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and its dependent claims, the phrase "thereby activating expression of a gene, or gene and gene product, that increases an immune recognition gene, or gene or gene product, or gene or gene product comprising ..." is unclear, and therefore it renders the claims indefinite. Is it the first referred gene or the second referred gene and gene product in the phrase that increases an immune recognition gene? Additionally, there is an improper Markush language in the phrase "comprising MAP kinase, NF kappa B, JAK, and STATS". Furthermore, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation "activating expression of a gene, or gene

and gene product" and the claim also recites "activation or posttranslational modification of a gene product comprising MAP kinase, NF kappa B, and STATS" which is the narrower statement of the range/limitation. Moreover, Claim 1 recites the limitation "posttranslational modification of a gene product" in lines 9 and 10 of the claim. There is insufficient antecedent basis for this limitation in the claim. In addition, the phrase "wherein activation is further involved in antigen presentation, growth, and function of the cell" is also unclear. Activation of what? Or activation of which gene or gene product recited in the claim. The metes and bounds of the claim as written can not be clearly determined. Clarification is requested.

Claim 2 recites the limitation "the gene or gene product" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. In claim 1 from which claim 2 is dependent upon, only gene and gene product is recited.

In claim 18, it is unclear what is encompassed by the phrase "the 90 kilodalton tumor-associated immunostimulator is an intermediate in the expression of the MHC class I molecule". What do Applicants exactly mean an intermediate? Since the term "intermediate" is not clearly defined in the specification, the metes and bounds of the claim can not be clearly determined.

Claims 21, 22, 26 and dependent claims of claim 26 (claims 75, 29, 30-33) recite the limitation "host organism" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of a host organism in claim 1 from which claims 21, 22, 26 and dependent claims of claim 26 are dependent upon.

In claim 74, there is an improper Markush language in the phrase "measuring an increase in expression of an MHC molecule or a costimulatory molecule, or an MHC molecule and a costimulatory molecule....".

Claim 75 and dependent claims 30-33 recite the limitation "the immunized host organism" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of an immunized host organism in claim 74 from which claim 75 and its dependent claims are dependent upon.

Claims 34 and 35 recite the limitation "the host animal" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any host animal in claim 74 from which claims 34 and 35 are dependent upon.

Claim 45 recites the limitation "the host organism" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any host organism in claim 13 or claim 1 from which claim 45 is dependent upon.

In claim 46, there is an improper Markush language in the phrase "measuring an increase in expression of a MHC molecule or a costimulatory molecule, or a MHC molecule and a costimulatory molecule involved in antigen presentation...". Additionally, the claim is incomplete because it lacks a step or steps connecting the steps (a) and (b) to presenting antigen to the immune system of a mammal. For example, there is no step of reintroducing a somatic mammalian cell with a double stranded polynucleotide into a mammal. Clarification is requested.

In claim 66, it is unclear what is encompassed by the phrase "the method of treatment is used to enhance another treatment method that enhances an immune response or an antigen presentation". How is it used? Which steps are involved in the use with another treatment method. The metes and bounds of the claim can not be clearly determined.

Claim 76 is incomplete because it lacks a step or steps connecting the steps (a)-(c) to treating cancer with a vaccine because there is no step for introducing the vaccine into a host with a cancer for treatment purpose. Clarification is requested. Similarly, claim 80 is incomplete for the same reason. Additionally, in claim 80, it is unclear what is encompassed by the phrase "is coordinate with a treatment with CpG residues". The metes and bounds of the claim can not be clearly determined because it is uncertain what is involved in the claimed method.

Claims 77 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those involved in increasing or decreasing the expression of antigen by the cell as recited in step (b). Otherwise, the metes and bounds of the claims can not be clearly determined.

Claims 81 and 82 are incomplete because they lack a step or steps connecting the steps (a)-(c) to treating a mammalian infectious disease which is associated with immunodeficiency recited in the preamble of the claims because there is no step for introducing the somatic mammalian cell containing a sequence of non-specific double-stranded polynucleotide into a host having an infectious disease which is associated

with immunodeficiency for treatment. Additionally, claim 81 recites the limitation "the somatic mammalian cell" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. Clarification is requested.

Claim 83 recites the limitation "the treatment involves activation or maturation of dendritic cells or peripheral blood macrophages pulsed with antigen in the form of protein, peptide, mRNA encoding antigen, or DNA encoding antigen from tumor cells" in lines 6-8 of the claim. What is the connection between this limitation with the recited steps (a) and (b)? There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-6, 13, 23, 25 and 44 rejected under 35 U.S.C. 102(b) as being anticipated by Stacey et al. (J. Immunology 157:2116-2122, 1996).

With respect to the enabled scope of the instant invention, Stacey et al. teach that bone marrow-derived macrophages and RAW 264 macrophage cells ingest bacterial plasmid DNA, synthetic dsDNA poly d(I-C) and ds RNA poly I.poly C and that the cells are activated leading to the activation of NF-kappa B and induction of a number of inflammatory genes including TNF-alpha (See abstract, page 2120, col. 2, last paragraph and Fig. 1). It is also well established that dsRNA is also capable of

inducing interferons, including beta-interferon in antigen presenting cells such as macrophages (page 2120, col. 2, first two lines of the last paragraph). Due to the inherent properties of activated macrophages, the expression of MHC molecules in the activated macrophages are also up-regulated for antigen presentation.

Therefore, Stacey et al. anticipates the instant claimed invention.

Claims 1-2, 4, 6, 10, 13, 16 and 74 rejected under 35 U.S.C. 102(b) as being anticipated by Henderson et al. (J. Immunology 159:635-643, 1997).

With respect to the enabled scope of the instant invention, Henderson et al. teach that upon phagocytosis of the bacterium *Mycobacterium tuberculosis in vitro* (a form of a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length) by immature human dendritic cells, the dendritic cells are activated by increased surface expression of the costimulatory molecules CD54, B7.1 as well as MHC class I molecules among other molecules. The infected DC also secrete inflammatory cytokines including TNFalpha, IL-1 and IL-12 (See abstract and Table 1).

Therefore, Henderson et al. anticipate the instant claims.

Claims 1-2, 4, 6, 8, 13 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuller et al. (AIDS Research and human retroviruses 10:1433-1441, 1994).

As written the claims encompass the teachings of Fuller et al. for which the instant specification has no support. Fuller et al. teach a method for the induction of *de novo* antigen production in the epidermis of BALB/c mice following particle bombardment of an expression vector encoding HIV-1 gp120 (double-stranded polynucleotide), resulting in both MHC class I- and class II-mediated antigen presentation for the elicitation of CTL and antibody responses, respectively (See abstract). The transfected immune cells in the epidermis must be activated to express MHC molecules in order to present the antigen of HIV-1 gp120 for inducing gp120-specific CTL and gp120-specific IgG responses.

Accordingly, Fuller et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stacey et al. (J. Immunology 157:2116-2122, 1996) in view of (Brakebusch et al., J. Biol. Chem. 272:3674-3682, 1997; PTO-1449, # 15).

With respect to the enabled scope of the instant invention, Stacey et al. teach that bone marrow-derived macrophages and RAW 264 macrophage cells ingest bacterial plasmid DNA, synthetic dsDNA poly d(I-C) and ds RNA poly I.poly C and that the cells are activated leading to the activation of NF-kappa B and induction of a number of inflammatory genes including TNF-alpha (See abstract, page 2120, col. 2, last paragraph and Fig. 1). It is also well established that dsRNA is also capable of inducing interferons, including beta-interferon in antigen presenting cells such as macrophages (page 2120, col. 2, first two lines of the last paragraph). It is also well known that the expression of MHC molecules is upregulated in activated macrophages for antigen presentation. Stacy et al. do not teach the introduction of plasmid DNA, ds RNA polyI.polyC into the macrophages by microinjection or direct injection using a needle or gene gun. Nor do Stacy et al. teach that the expression of MHC molcule is accompanied by increased expression of an about 90 kilodalton tumor-associated immunostimulator. However, Brakebush et al. teach that dsRNA polyI.polyC can induce the expression of 90 kilodalton tumor-associated immunostimulator (See abstract).

At the time of the instant invention was made, it would have been obvious to an ordinary skilled artisan to modify the method taught by Stacy et al. by introducing the

plasmid DNA, dsRNA polyI.polyC by microinjection or direct injection using a needle or gene gun. One of ordinary skilled in the art would have been motivated to carry out such a modification because it is just a matter of designer's choice, and it is well within the scope of skills for an ordinary skilled artisan. In addition, in view of the teachings of Brakenbush et al., the activated macrophages ingesting dsRNA polyI.polyC would also have an increased expression of 90 kilodalton tumor-associated immunostimulator.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER